

Dioxin and Diabetes in Ranch Hand Veterans

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- Review
- The elimination rate hypothesis
- The lipid binding hypothesis
- Insulin vs dioxin exposure category
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Review

- Goal: To conduct a 20-year prospective epidemiological study of herbicide exposure and health, mortality, and reproductive outcomes in veterans of Operation Ranch Hand

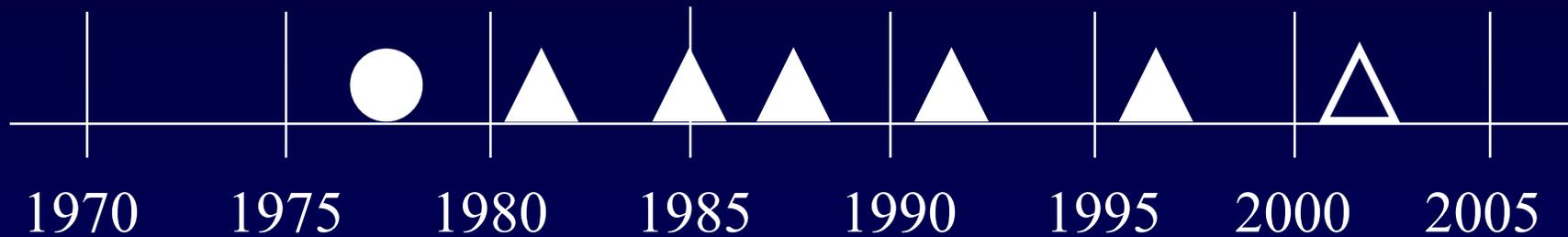
Study Design

- Index group: Ranch Hand veterans (N=1,208)
- Control population: Air Force veterans of Southeast Asia (N=19,080)
- Examined controls matched on age, race, military occupation (N=1,668)

Study Design (Continued)

- Exposure index: dioxin body burden
- Multiple endpoints
- Repeated physical examinations, interviews and mortality assessments

Schedule



Protocol Development



Physical Examination Completed



Physical Examination Scheduled

Sample Sizes in 1997

Stratum	Ranch Hand	Comparison
Officer	341	494
Enlisted flyer	151	187
Enlisted ground	378	570
Total	870	1,251

Dioxin Exposure Category

Category	Definition*	N
Comparison	$D \leq 10$	1,213
RH Background	$D \leq 10$	381
RH Low	$D > 10, I \leq 94$	239
RH High	$D > 10, I > 94$	243

*D=dioxin (ppt), I=extrapolated initial dioxin (ppt)

Demographic Characteristics

June 1995

Ranch Hand

Mean	Comp (N=1,276)	Bkg (N=422)	Low (N=284)	High (N=283)
Dioxin	4.0	5.7	52.7	197.5
Age	53.5	54.6	54.9	50.9
PBF	21.8	20.2	22.2	23.4

Military Occupation (%)

June 1995

Ranch Hand

	Comp (N=1,276)	Bkg (N=422)	Low (N=284)	High (N=283)
Officer	38.5	61.6	38.0	2.5
En flyer	16.1	11.6	21.5	20.8
En grnd	45.4	26.8	40.5	76.7

Diabetes Mellitus to June 1995*

Ranch Hand

	Comp (N=1,276)	Bkg (N=422)	Low (N=284)	High (N=283)
N (%)	169 (13.2)	40 (9.5)	49 (17.2)	57 (20.1)
RR	1.0	0.7	1.3	1.5
95% CI		0.5, 1.0	1.0, 1.7	1.2, 2.0

*Henriksen et al (1997)

Diabetes Mellitus to June 1998*

Ranch Hand

	Comp (N=1,195)	Bkg (N=379)	Low (N=235)	High (N=240)
N (%)	199 (16.7)	37 (9.8)	49 (20.9)	57 (23.8)
RR	1.0	0.7	1.2	1.5
95% CI		0.5, 1.0	0.8, 1.8	1.0, 2.2

*Michalek et al (2000)

The Elimination Rate Hypothesis

H_1 : The association between diabetes and dioxin represents an association between diabetes and dioxin elimination
(and is therefore artifactual)

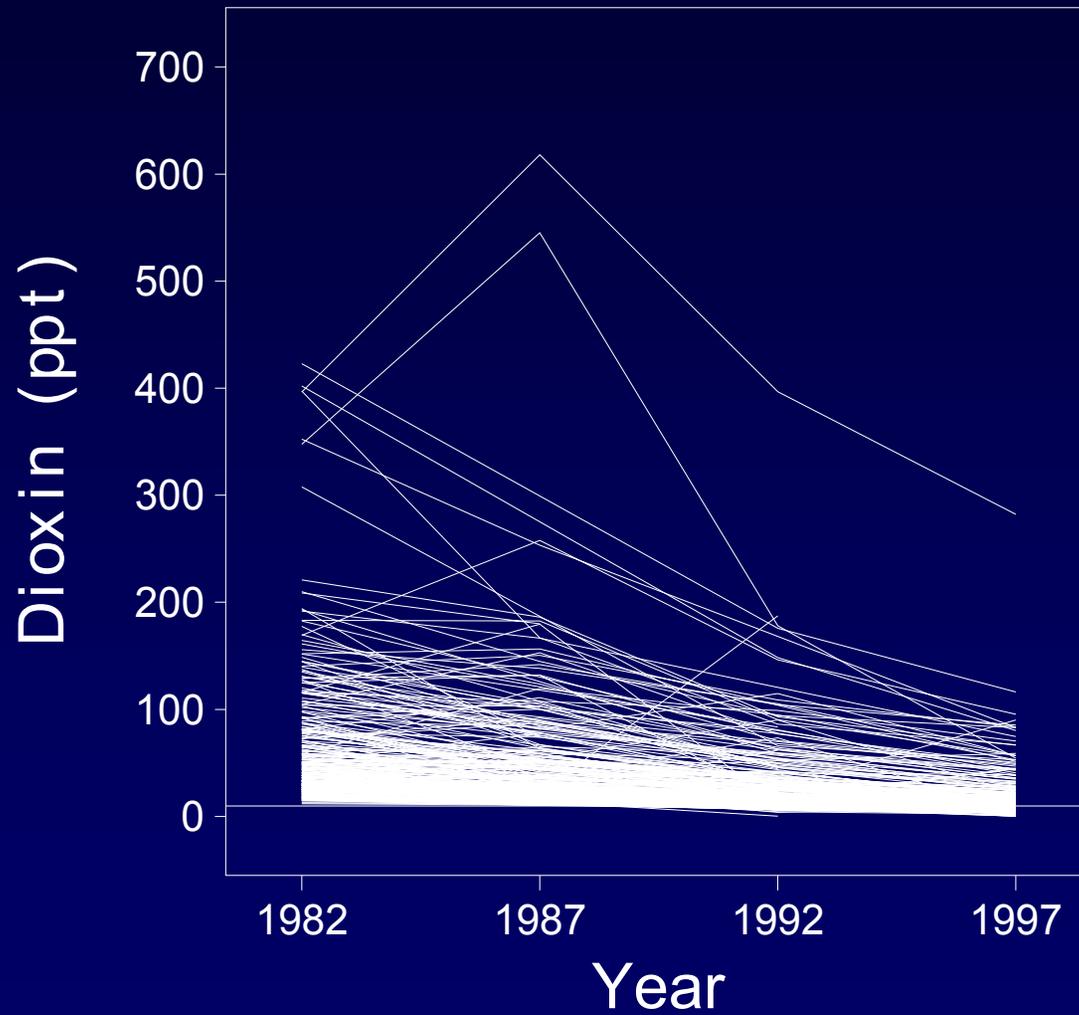
Elimination Rate Materials

- 343 Ranch Hand veterans with dioxin > 10 ppt in 1982 and 1987
- Described in Michalek, Pirkle, Caudill et al *J Toxicol Environ Health* 1996;47:209-229
- 1 Pre-SEA diabetic excluded
- 95 of 342 (27.8%) are diabetic

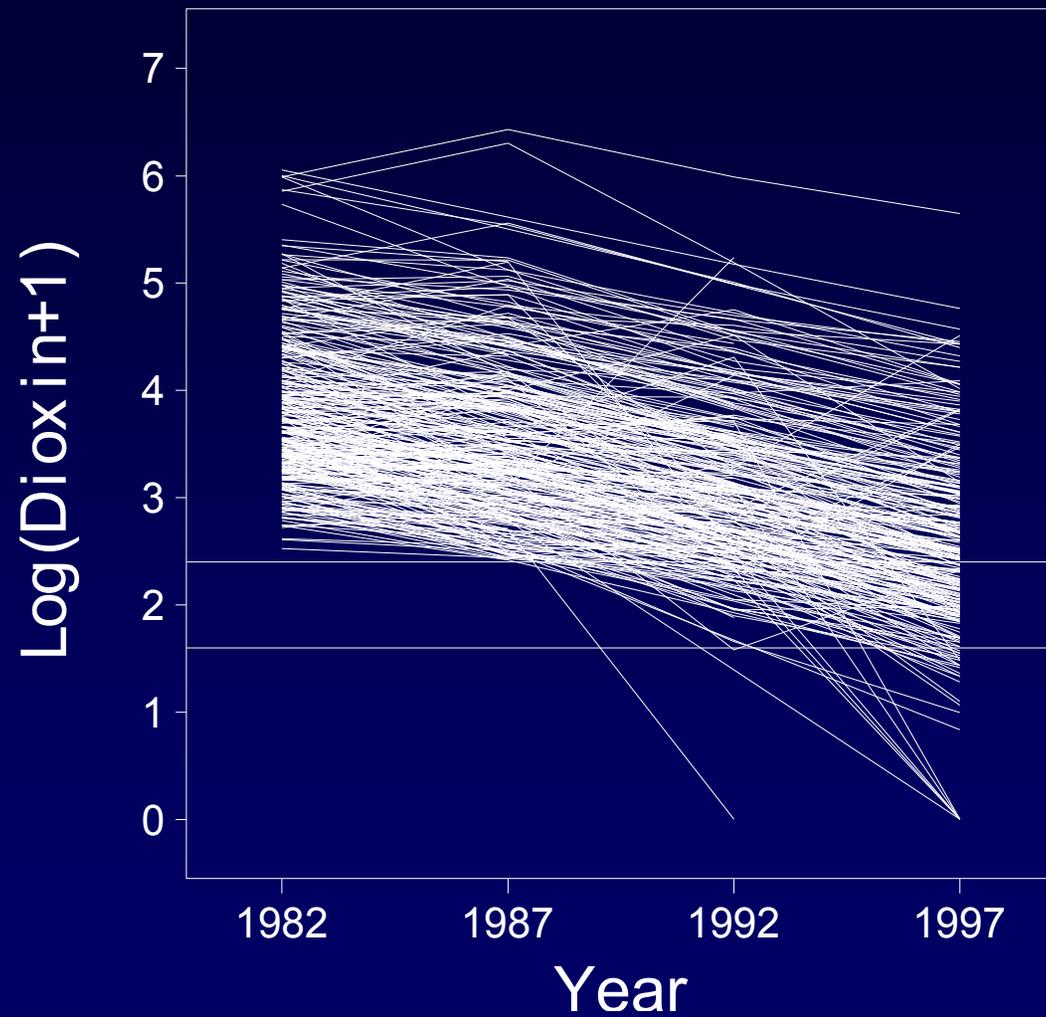
Repeated Dioxin Measurements

1982	1987	1992	1997	n	N
yes	yes	no	no	26	26
yes	yes	no	yes	39	65
yes	yes	yes	no	34	99
yes	yes	yes	yes	244	343

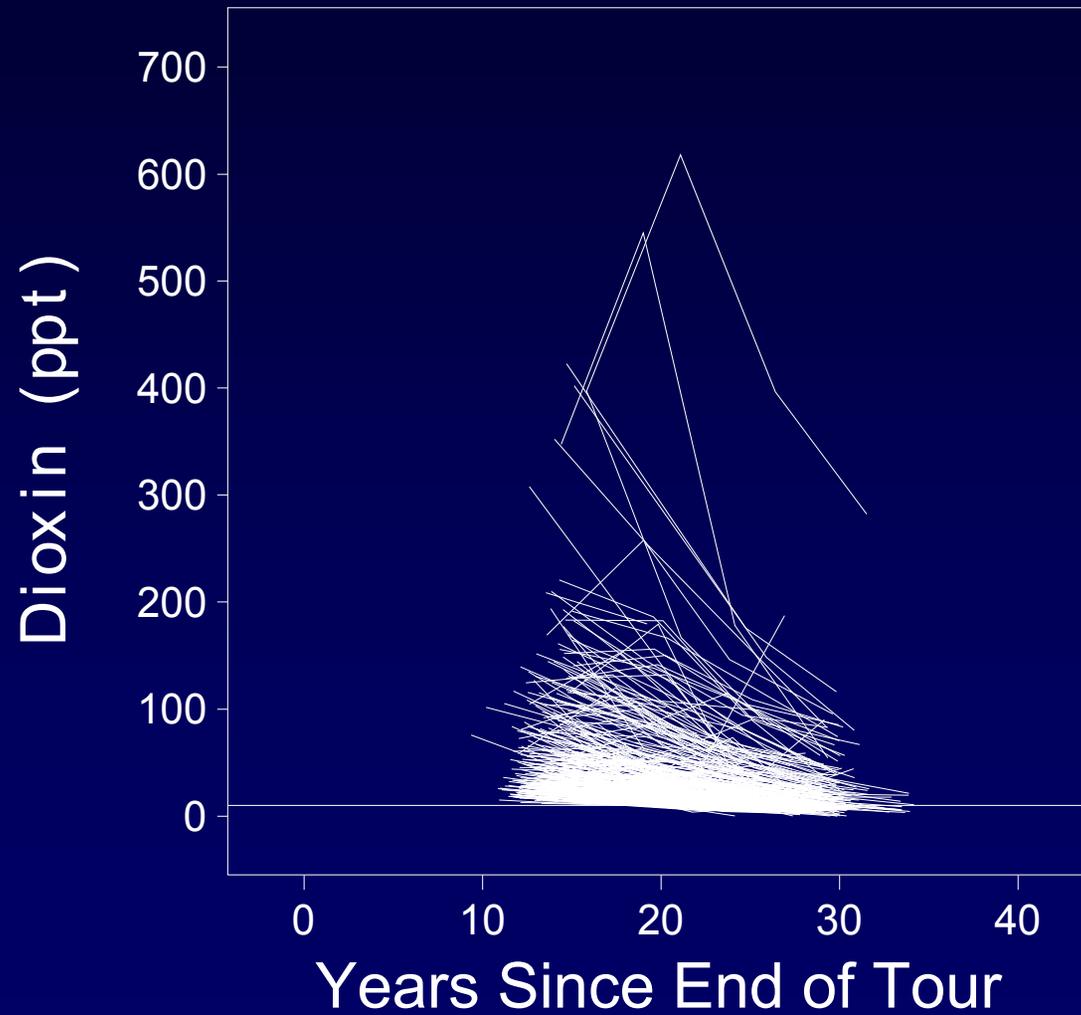
Dioxin (ppt) by Year (N=343)



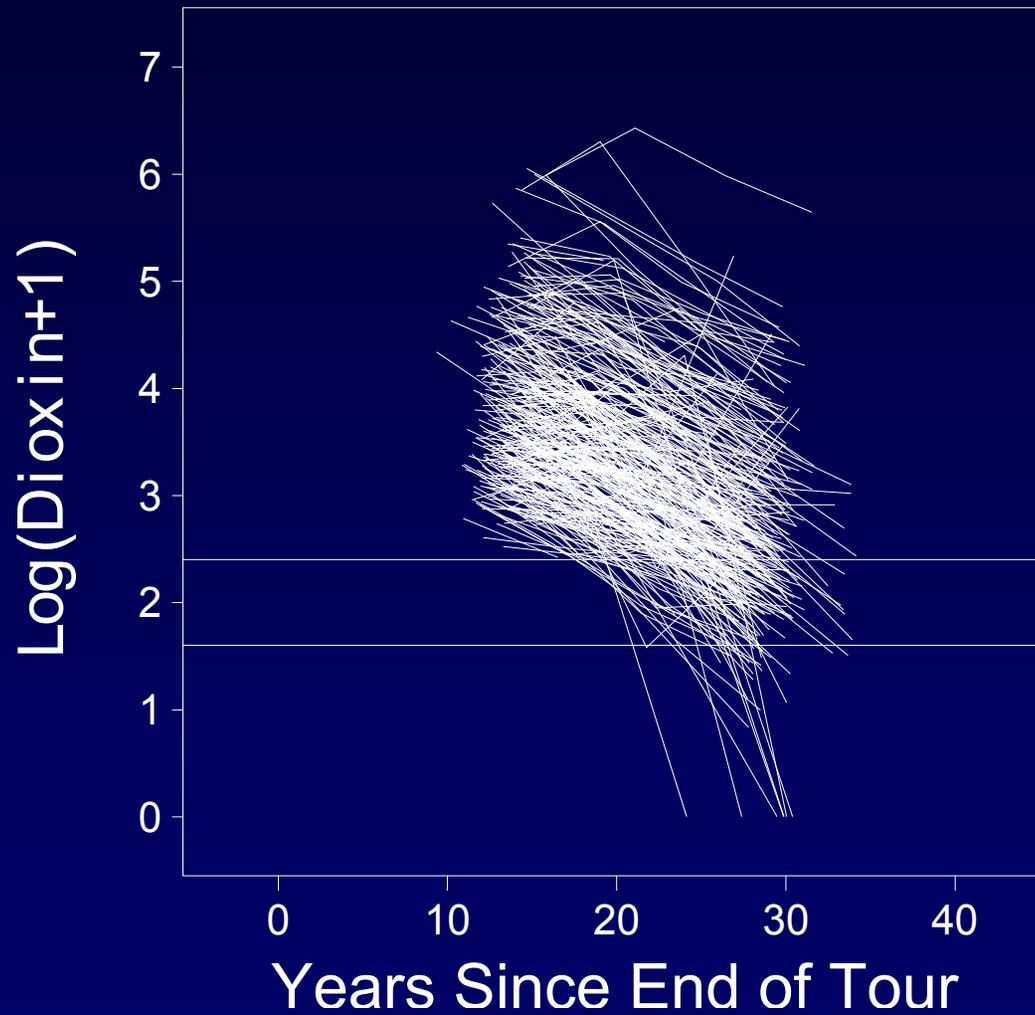
Log(Dioxin+1) by Year (N=343)



Dioxin (ppt) vs Years Since Tour



Log(Dioxin+1) vs Years Since Tour



Statistical Models

$$C_t = C_0 e^{-\lambda t}$$

$$\log(C_t) = \log(C_0) - \lambda t$$

$$y_{ij} = \mu + \tau_i + \beta_1 t_{ij} + \varepsilon_{ij}, i = 1, \dots, n, j = 1, \dots, k$$

$$\beta_1 = -\lambda$$

$\mathbf{y}_i \approx$ Multivariate normal k, Σ

Weighted Least Squares Estimate of the Elimination Rate (λ) for the i^{th} Subject

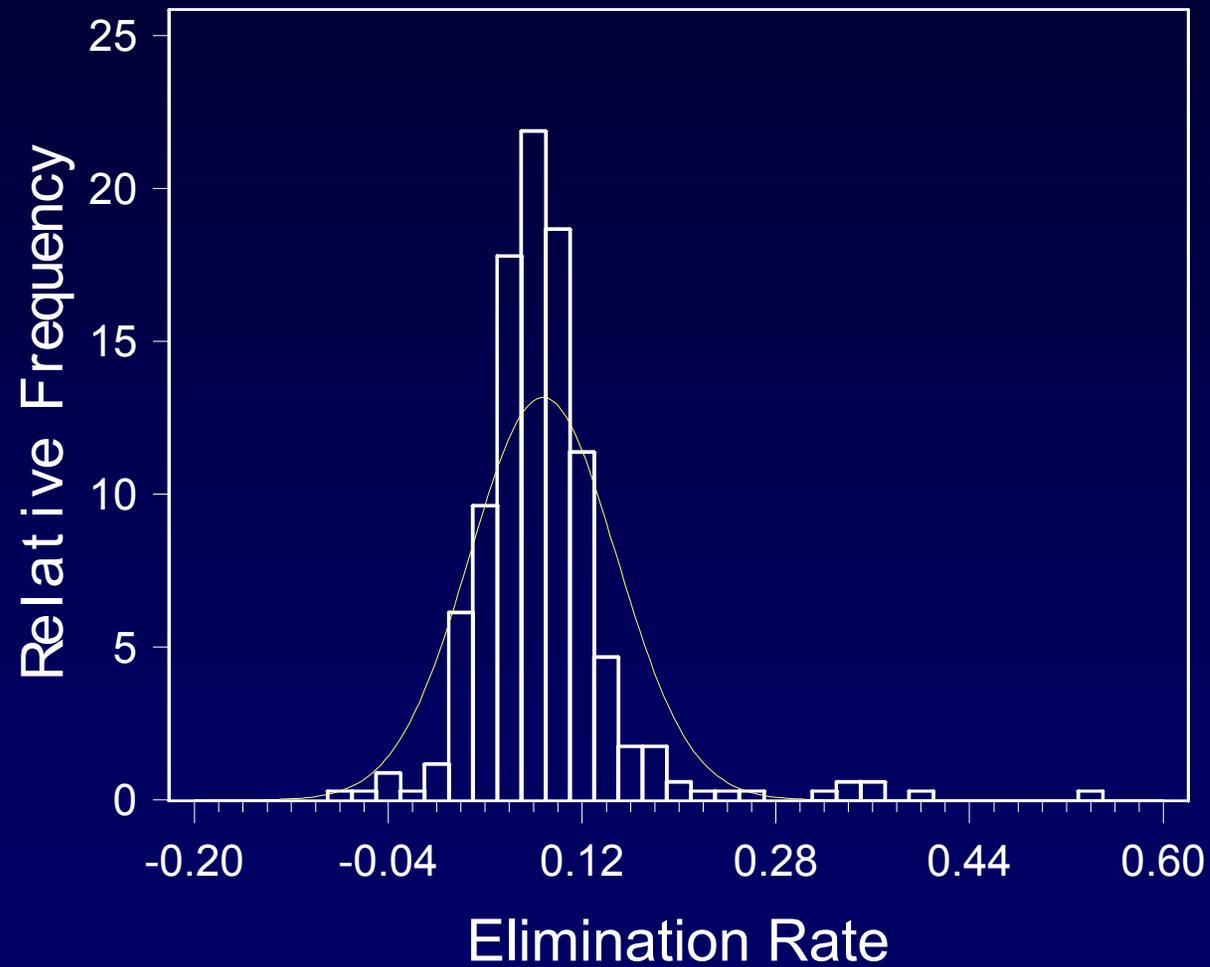
$$\lambda_i = w_{i12} \lambda_{i12} + w_{i13} \lambda_{i13} + w_{i23} \lambda_{i23}$$

$$\lambda_{ijk} = (y_{ij} - y_{ik}) / \Delta_{ijk}, \Delta_{jk} = t_{ik} - t_{ij}$$

$$w_{ijk} = \Delta_{ijk}^2 / \left[\frac{1}{n} \sum_{i=1}^n (\Delta_{i12}^2 + \Delta_{i13}^2 + \Delta_{i23}^2) \right]$$

$$y_{ij} = \log(\text{dioxin}_{ij} + 1)$$

Elimination Rate Distribution (N=343)



Statistical Modeling

Proportional hazards

$$h(t | \lambda) = h_0(t) e^{\beta\lambda}, \quad t = \text{time to diabetes onset}$$

Logistic Regression

$$p(\text{diabetes} | \lambda) = \frac{e^{\beta_0 + \beta_1 \lambda}}{1 + e^{\beta_0 + \beta_1 \lambda}}$$

Linear

$$\lambda = \beta_0 + \beta_1 x + \varepsilon, \quad x = I(\text{diabetes})$$

Proportional Hazards

Source	Coefficient	p-value
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λ	-0.03	0.15
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Proportional Hazards

Source	Coefficient	p-value
λ	-0.02	0.28
Age	0.06	<0.001

Proportional Hazards

Source	Coefficient	p-value
λ	-0.002	0.91
Age82	0.06	<0.001
PBF82	0.09	<0.001

Proportional Hazards

Source	Coefficient	p-value
λ	0.005	0.80
Age82	0.06	<0.001
PBFT	0.18	<0.001
RELCH	0.17	0.002

Proportional Hazards

Source	Coefficient	p-value
λ	0.008	0.69
LogDx	0.22	0.01
Age82	0.07	<0.001
PBFT	0.18	<0.001
RELCH	0.18	<0.001

Matched Pair Testing on Diabetes (RR=1.6, 95% CI 1.2 to 2.0, p<0.001)

Comparison

	Diabetes	No	Yes	Total
Ranch Hand	No	208	39	247
	Yes	73	22	95 (27.8%)
	Total	281	61 (17.8%)	342

Matched Pair Testing on 1997 Insulin
($\mu\text{IU/ml}$) in Non-diabetics (183 pairs)
($p=0.03$ in log units)

	Mean	Std Err
Ranch Hand	78.1	6.9
Comparison	62.0	4.3

The Lipid Binding Hypothesis

H₁: Dioxin binds differentially to lipid fractions and therefore the relation between dioxin and diabetes interacts with lipid concentrations

Lipid Binding Materials

- 989 Ranch Hands and 1,276 Comparisons with dioxin levels, diabetes information, and covariates
- Described in
 - Henriksen et al, *Epidemiology* 1997;8:252-258
 - Michalek, *Epidemiology* 1998;9:359-360

Diabetes Mellitus to June 1995 Adjusted for Triglycerides*

Ranch Hand

	Comp (N=1,276)	Bkg (N=422)	Low (N=284)	High (N=283)
N (%)	169 (13.2)	40 (9.5)	49 (17.2)	57 (20.1)
RR	1.0	0.7	1.3	1.4
95% CI		0.5, 1.0	1.0, 1.8	1.1, 1.8

*Michalek (1998)

Diabetes vs Whole Weight Dioxin

Main Effects Model

Source	Coefficient	p-value
Intercept	-2.6311	
LogWWDx*	0.1810	0.001
Triglycerides	0.00237	<0.001
Birth Year	-0.0740	<0.001
PBF	0.1065	<0.001

*Whole weight dioxin

Diabetes vs Whole Weight Dioxin Interaction Model

Source	Coefficient	p-value
Intercept	-2.8939	
LogWWDx*	0.2480	0.002
Triglycerides	0.00405	0.008
LogWWDx by Triglycerides	-0.00037	0.24
Birth Year	-0.0740	<0.001
PBF	0.1053	<0.001

*Whole weight dioxin

Insulin versus Dioxin Category in Non-Diabetic Veterans

The risk of abnormally high insulin is significantly increased in the High dioxin exposure category

Insulin Normal Ranges ($\mu\text{IU/ml}$)

- 1997 report (Scripps Clinic): 18-56
- 1992 (2.5, 97.5 Comparison percentiles)*
 - nondiabetic: 14-346
 - fasting diabetic: 7-189
 - nonfasting diabetic: 20-528
- 1997 (2.5, 97.5 Comparison percentiles)
 - nondiabetic: 6-256

*Henriksen et al (1997)

1997: Insulin vs Dioxin Category Nondiabetic, Abnormally High*

	Comp (N=985)	Bkg (N=334)	Low (N=183)	High (N=181)
Abn (%)	21 (2.1)	7 (2.1)	11 (6.0)	8 (4.4)
OR	1.0	1.1	2.6	2.6
95% CI		0.4, 2.4	1.2, 5.7	1.0, 6.3

*97.5% Comparison percentile

1997: Insulin vs Dioxin Category Nondiabetic, Abnormally High*

	Comp (N=996)	Bkg (N=342)	Low (N=186)	High (N=183)
Abn (%)	418 (42.0)	122 (35.7)	85 (45.7)	87 (47.5)
OR	1.0	1.0	1.0	0.9
95% CI		0.7, 1.3	0.7, 1.4	0.7, 1.4

*Scripps cut point (Table 16-21)

1997: Insulin vs Dioxin Category Nondiabetic, Abnormally Low*

	Comp (N=966)	Bkg (N=331)	Low (N=172)	High (N=173)
Abn (%)	2 (0.21)	4 (1.2)	0 (0.0)	0 (0.0)
OR	1.0	5.1		
95% CI		0.9, 28.8		

*2.5% Comparison percentile

1997: Insulin vs Dioxin Category Nondiabetic, Abnormally Low*

	Comp (N=996)	Bkg (N=342)	Low (N=186)	High (N=183)
Abn (%)	131 (13.2)	51 (14.9)	20 (10.8)	13 (7.1)
OR	1.0	0.9	0.8	0.6
95% CI		0.6, 1.31	0.5, 1.4	0.3, 1.1

*Scripps cutpoint (Table 16-21)

The Diabetes Check Mark Pattern

Overall RR=1 and a statistically
significant positive trend in the
Ranch Hand group

The Check Mark Pattern

- Predicted in terms of the Mahalanobis distance (D) on the log scale
- $X = \log(\text{dioxin} + 1)$
- $D = (\mu_R - \mu_C) / \sigma$
- $p(\text{diabetes} | X) = e^{\alpha + \beta X} / (1 + e^{\alpha + \beta X})$
- $E(p) = E[p(X)]$

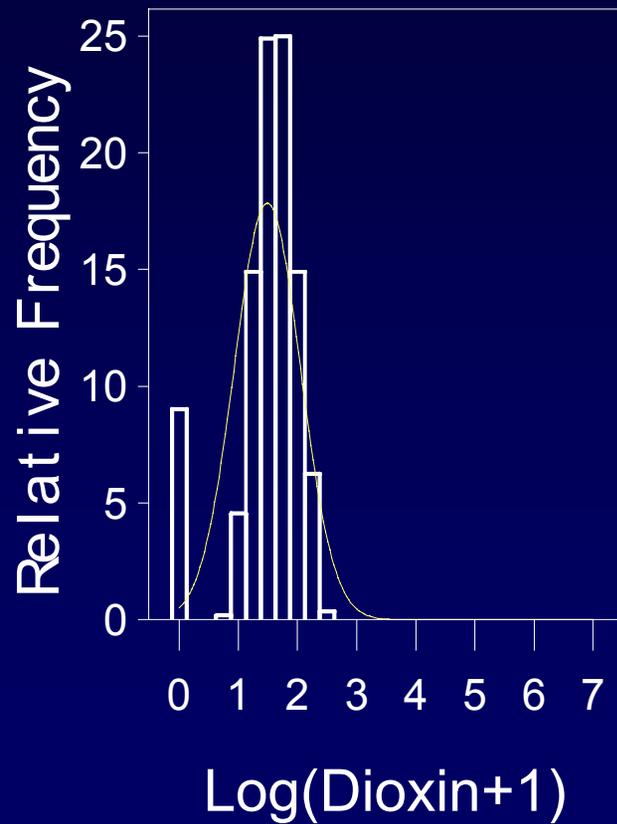
Computing the Expected Pattern

Expected disease prevalence in the Background category:

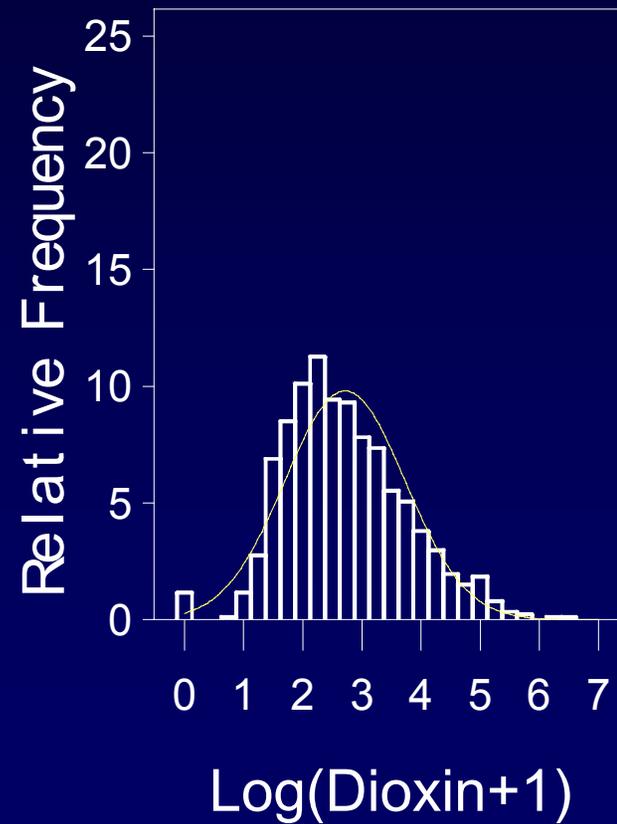
$$E[p(X)] = \frac{\frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^c \frac{e^{\alpha+\beta x}}{1+e^{\alpha+\beta x}} e^{-\frac{(x-\mu)^2}{2\sigma^2}} dx}{\frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^c e^{-\frac{(x-\mu)^2}{2\sigma^2}} dx}$$

Dioxin Distributions in Log Units

Comparison



Ranch Hand

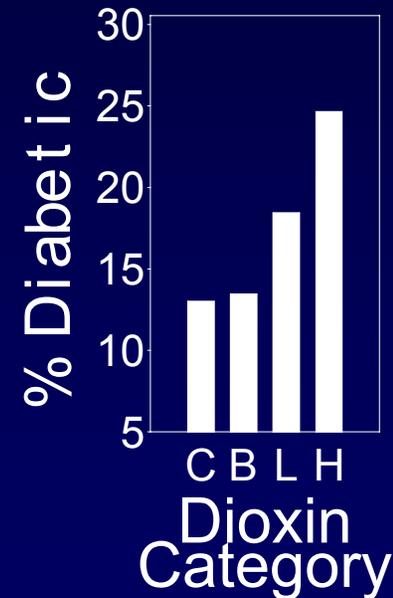
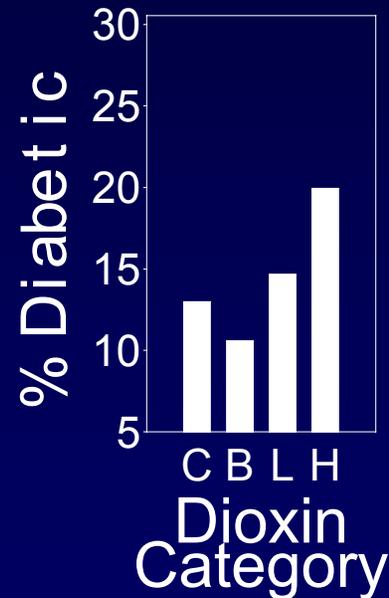
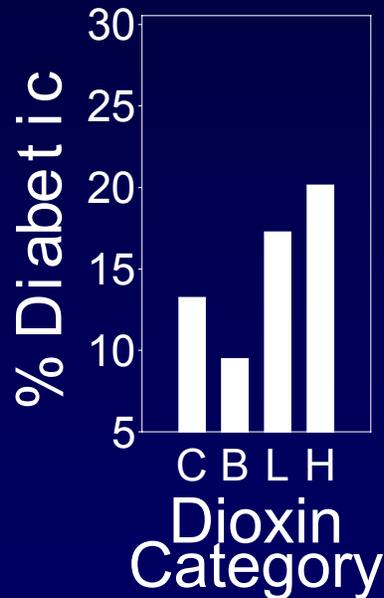


The Diabetes Check Mark Pattern*

Obs

Exp (D=1.5)

Exp (D=2.5)



*Obs=Observed (Henriksen et al 1997), Exp=Expected

Web Page

www.brooks.af.mil/AFRL/HED/hedb/afhs.html